GNOSIS: Guidelines for neuro-oncology: Standards for investigational studies—reporting of phase 1 and phase 2 clinical trials

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We present guidelines to standardize the reporting of phase 1 and phase 2 neuro-oncology trials. The guidelines are also intended to assist with accurate interpretation of results from these trials, to facilitate the peer-review process, and to expedite the publication of important and accurate manuscripts. Our guidelines are summarized in a checklist format that can be used as a framework from which to construct a phase 1 or 2 clinical trial. *Neuro-Oncology 7, 425–434, 2005 (Posted to Neuro-Oncology [serial online], Doc. 05-055, August 25, 2005. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152851705000554)*

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[3]Abbreviations used are as follows: EIAEDs, enzyme-inducing antiepileptic drugs; PK, pharmacokinetic.

Development of new treatments in oncology is made possible by the design, conduct, and reporting of prospective clinical trials. The phase 3 randomized, controlled clinical trial is considered to be the "gold standard" of clinical research, providing the most reliable method for comparing standard with experimental therapies. However, most clinical reports in the neuro-oncology literature are of phase 1 and phase 2 trials, which are required for testing the safety and efficacy of a proposed drug before the initiation of a phase 3 study. Incomplete, unclear, or inaccurate design, interpretation, and reporting of the results from these vital early phase trials can hamper timely drug development and lead to erroneous conclusions as to efficacy (Mariani and Marubini, 2000).

Recently, there has been a trend in the scientific community toward the creation of guidelines for increasing the transparency of clinical study results. Some examples of these guidelines include the STARD, or Standards for Reporting of Diagnostic Accuracy, statement for reporting studies of diagnostic accuracy (Bossuyt et al. 2003), the TREND, or Transparent Reporting of Evaluations with Nonrandomized Designs, statement for reporting nonrandomized public health interventions (Des Jarlais et al., 2004), and most familiar, the CONSORT, or Consolidated Standards of Reporting Trials, statement

for the reporting of randomized, controlled clinical trials (Altman et al., 2001). The CONSORT statement has particular relevance to neuro-oncology. However, as it deals exclusively with phase 3 trials, it does not address many important issues that arise in the reporting of phase 1 and phase 2 neuro-oncology trials.

In this document, we present guidelines to promote standardized reporting for phase 1 and phase 2 neuro-oncology trials and to assist the neuro-oncology community with accurate interpretation of results from these trials, thereby facilitating the peer-review process and expediting the publication of important and accurate manuscripts. Our guidelines are summarized in a checklist format that can also be used as a framework from which to construct a phase 1 or 2 clinical trial. Several items from the CONSORT statement (Altman et al., 2001) have been used with permission.

These recommendations do not include a comprehensive review of neuro-oncology clinical trial methodology; a working knowledge of the basics of phase 1 and 2 trial design and conduct is assumed. We also acknowledge that new insights into disease biology, treatment outcomes, and technology development require new clinical-trials methodology. Nevertheless, these guidelines serve as a starting point for transparent reporting of phase 1 and 2 neuro-oncology trials.

Explanation of the Phase 1 and Phase 2 Checklists

The following sections expand on the checklists presented in Tables 1 and 2, and selected subsections are enumerated to reflect the corresponding items in the checklists. In many instances the specific consideration is relevant to both phase 1 and phase 2 trials; those that pertain to either one or the other are set in boldface as they occur. *Some items on the checklists are considered self-explanatory and are not expanded upon in the body of this document. Not all checklist items will be applicable to all clinical trials.* We also acknowledge that individual journals may require specific formatting for the sections of a paper.

Title

The phrases used in the title are important for accurate retrieval of an article in biomedical indices such as Medline. Title words should include the specific tumor type (using 2000 WHO terminology; Radner et al., 2002), the intervention studied, the status of the disease (newly diagnosed/recurrent), the population studied (adult/pediatric), and whether pharmacokinetic studies were performed.

Abstract

The Abstract should summarize the Introduction, Methods, Results, and Conclusions. A structured summary is recommended (Ad Hoc Working Group for Critical Appraisal of the Medical Literature, 1987; Haynes et al., 1990) if this format is compatible with the publisher's specifications. Keywords used in the abstract are also important for accurate retrieval of an article in biomedical indices such as Medline.

Introduction

The Introduction should be concise and provide a summary of the information leading up to the current study. The biologic basis and/or clinical rationale for the intervention should be provided. For example, if the trial evaluates a new pharmacologic agent, the mechanism of action of the new drug must be documented, that is, whether the new agent is a cytotoxic drug or novel agent with a cytostatic or targeted mechanism. The rationale for selection of this agent for the patient population should be clearly presented, including results of preclinical work specific to brain tumors. Any known pharmacokinetic (PK)[3] information, including CNS penetration and known drug interactions, as well as prior clinical PK results in patients, should be presented. In addition, for **phase 2** studies, clinical experience in patients with brain tumors with respect to known toxicity should also be summarized. For pediatric **phase 1** studies, adult data concerning the potential utility and toxicity of the drugs should be included.

An important consideration in brain tumor clinical trials is the potential influence of drug interactions on the pharmacokinetics of chemotherapeutic drugs. Such drug interactions may alter the type and severity of toxicities that patients experience (Vecht et al., 2003). An example of such an interaction is seen with the administration of enzyme-inducing antiepileptic drugs (EIAEDs), which are metabolized by the hepatic cytochrome p450 enzyme system. It has been shown that patients taking paclitaxel or CPT-11 while taking EIAEDs may have lower than expected plasma levels and higher than expected tolerated doses (Chang et al., 2001; Prados et al., 2004). Thus, studies of agents metabolized by this enzyme system should report if there was stratification of patients based on EIAED use. Some phase 2 brain-tumor studies currently allow only patients who are not on EIAEDs to be enrolled, with a plan to conduct a phase 1 study to define the phase 2 dose for patients on EIAEDs if any antitumor activity is seen. For studies restricted to patients who are not on EIAEDs, the guidelines used for tapering patients off of EIAEDs and onto non-enzyme-inducing antiepileptic agents should be clearly described.

In addition to the rationale for the trial, a succinct statement of the primary purpose of the trial should be included. For **phase 1 trials**, the most common purpose is to identify the appropriate dose, schedule, and toxicity of a novel intervention. For **phase 2 trials**, the most common purpose is to estimate whether there appears to be a clinically relevant level of efficacy for the intervention in a defined cohort of patients. Increasingly, for a new agent, a component of the evaluation at this stage is a proof of concept to determine if there is a detectable biologic effect on the intended molecular target. In addition, analysis of the safety and feasibility of the intervention is continued from phase 1 studies.

Table 1. Phase 1 checklist*

Section of Report	Item	Description
Title	1	☐ Phase 1 trial, intervention studied, newly diagnosed or recurrent tumor, tumor type, study population
		☐ State if PK studies are part of the research.
Abstract	2	☐ Structured abstract recommended, consisting of Introduction, Methods, Results, and Conclusions
Introduction	3	Scientific background and explanation of rationale
		☐ Drug background information: name, trademarked name, mechanism of action
		Rationale for trial/preclinical efficacy of study drug
		☐ In vitro studies
		☐ In vivo studies
		☐ Phase 1 studies in other tumor types
		☐ Any known PK information, especially regarding CNS penetration and the role of drug interactions
Methods		
• Eligibility criteria	4	☐ Age
		☐ Performance status
		☐ Estimated survival
		☐ Laboratory tests (required counts/levels/functions)
		☐ Informed consent and IRB approval
		☐ Newly diagnosed/recurrent tumor
		☐ If recurrent, state criteria for determining progression.
		☐ Measurable versus nonmeasurable evaluable disease
		☐ Surgical/radiographic criteria to confirm tumor if focal high-dose radiation was used previously
		☐ Tumor type/grade/stage: Use 2000 WHO scale
		☐ Histology review: Note if central review was required.
		☐ Prior treatment (resection/radiation/chemotherapy)
		☐ Number of prior treatments/relapses allowed
		☐ Recovery period after prior treatment
		☐ Comorbidity
		☐ Altered drug metabolism
		☐ EIAEDs
		☐ Steroids
		☐ Other drugs
		☐ Other exclusion criteria specific to agent/trial
• Treatment plan	5	☐ Setting and location of data collection
		☐ Stratification, if relevant
		☐ Treatment plan with definition of cycles and duration of treatment
		☐ Medications that should not be given concurrently
		☐ Supportive care allowed
		☐ Concurrent radiation treatment regimen, if applicable
		☐ Criteria for removal from study
		☐ Dose escalation
		☐ Toxicity criteria (NCI current version)
		☐ Definition of AEs, DLTs, and MTD
		☐ Plan for escalation
		☐ Time for assessment before escalation
		☐ Data safety monitoring plan (AdEERS)
		☐ Conditions for replacement of patients
• Study requirements	6	☐ Laboratory monitoring (including frequency)
		☐ Radiographic monitoring (including frequency)
		☐ Imaging modalities allowed
		☐ Neurological monitoring (including frequency)
		☐ Specify if PK studies also performed.

Table 1. (continued)

Section of Report	Item	Description
• Assessment of efficacy	7	☐ Supplementary end point definitions, e.g., response rate, 6-month PFS ☐ If response is an end point, reference to the MacDonald criteria should be made, with specific mention of steroid dosing. ☐ Note central review of imaging.
• Statistical methods	8	☐ Descriptive information summary relevant to phase 1 design ☐ Statement of probability of observing an adverse event ☐ State source of analysis (authors, institution, or industry).
Results		
• Patient flow	9	☐ Dates defining recruitment and follow-up ☐ Number of patients accrued ☐ Number of patients replaced ☐ Number of patients that completed the study ☐ Reasons for discontinuation of treatment ☐ Number of patients that were lost to follow-up ☐ Protocol violations from study as planned; reasons
• Baseline data	10	☐ Demographic and clinical data in tabular form
• Number of patients treated at various dose levels	11	☐ Number of patients included in each cohort in tabular form
• Outcome	12	☐ DLTs encountered and MTD determined: Use tabular form for toxicities ☐ All SAEs encountered ☐ Duration of treatment ☐ If activity is a secondary end point, note responses and tumor types.
• Ancillary analyses	13	☐ Summary of other analyses performed and whether they were prespecified or exploratory, e.g., PK results
Discussion		
• Interpretation	14	☐ Interpretation of results taking into account study hypotheses, sources of potential bias, limitations or weaknesses of the study
• Expected versus observed	15	☐ Discussion of results in the context of what was expected and what was actually seen based on other phase 1 studies if applicable
• Overall evidence	16	☐ Include general interpretation of the results in context of current evidence and theory.
• Future directions	17	☐ Based on results, is the therapy safe enough to justify further study/research? ☐ Future directions for the agent studied, if any
Acknowledgments		
• Disclosure	18	☐ Financial disclosure and any potential conflict of interest of the authors ☐ Trial sponsor

Abbreviations: AdEERS, Adverse Event Expedited Reporting System; AE, adverse event; DLT, dose-limiting toxicity; EIAEDs, enzyme-inducing antiepileptic drugs; IRB, institutional review board; MTD, maximum tolerated dose; PFS, progression-free survival; PK, pharmacokinetic; SAE, severe adverse event

*Not all checklist items will apply to all studies. Several checklist items have been taken from the CONSORT statement (Altman et al., 2001) with permission (also available at http://www.consort-statement.org).

Table 2. Phase 2 checklist*

Section of Report	Item	Description
Title	1	☐ Phase 2 trial, intervention studied, newly diagnosed or recurrent tumor, tumor type, study population
		☐ State if PK studies are part of the research.
Abstract	2	☐ Structured abstract recommended, consisting of Introduction, Methods, Results, and Conclusions
		☐ In the abstract Introduction, state the type of phase 2 study: e.g., open-labeled, nonrandomized, single arm.
Introduction	3	Scientific background and explanation of rationale
		☐ Drug background information: name, trademarked name, mechanism of action
		Rationale for trial
		Preclinical efficacy of study drug
		☐ In vitro studies
		☐ In vivo studies
		Clinical efficacy of study drug
		☐ Phase 1 studies in brain tumors
		☐ Prior clinical experience with drug/known toxicities
		☐ PK profile
Methods		
• Eligibility criteria	4	☐ Age
		☐ Performance status
		☐ Estimated survival
		☐ Laboratory tests (required counts/levels/functions)
		☐ Informed consent and IRB approval
		☐ Newly diagnosed/recurrent tumor
		☐ If recurrent, state criteria for determining progression.
		☐ Measurable versus nonmeasurable evaluable disease
		☐ Surgical/radiographic criteria for confirmation of tumor if focal high-dose radiation was used previously
		☐ Tumor type/grade: Use 2000 WHO scale
		☐ Histology review: Note if central review was required.
		☐ Prior treatment (resection/radiation/chemotherapy)
		☐ Number of prior treatments/relapses allowed
		☐ Recovery period after prior treatment
		☐ Comorbidity
		☐ Altered drug metabolism
		☐ EIAEDs
		☐ Steroids
		☐ Other drugs
		☐ Other exclusion criteria specific to agent/trial
• Treatment plan	5	☐ Setting and location of data collection
		☐ Stratification, if relevant
		☐ Dosage/number of cycles
		☐ Medications that should not be given concurrently
		☐ Supportive care allowed
		☐ Dose modifications (toxicities)/reescalations allowed
		Use NCI criteria for toxicities.
		☐ Concurrent radiation treatment regimen, if applicable
		☐ Criteria for removal from study
		☐ Data safety monitoring plan (AdEERS)
		☐ Early stopping rules
		☐ Conditions for replacement of patients
• Study requirements	6	☐ Laboratory monitoring (including frequency)
		☐ Radiographic monitoring (including frequency)
		☐ Imaging modalities allowed
		☐ Neurological monitoring (including frequency)
		☐ Specify if PK studies also performed.

Table 2. (continued)

Section of Report	Item	Description
• Assessment of efficacy	7	☐ Criteria for evaluation and rationale for primary end point definitions, e.g., progression-free survival, time to progression
		☐ If response is an end point, reference to the MacDonald criteria should be made, with specific mention of steroid dosing.
		☐ Note central review of imaging.
		☐ Note if scan was required to confirm response.
		☐ Details on measurement of effect
• Statistical methods	8	☐ Decision rule for determining success
		☐ Hypothesis and justification of sample size based on expected effect versus historical control (power calculation)
		☐ Specify design (e.g., one or two stage).
		☐ Statistical methods used to compare study group to historical control
		☐ Statistical methods used for additional analyses
		☐ Methods for dealing with missing data
		☐ Statistical software or programs used
		☐ State source of analysis (authors, institution, or industry).
Results		
• Patient flow	9	☐ Dates defining recruitment and follow-up of study
		☐ Number of patients accrued
		☐ Number of patients ineligible
		☐ Duration of treatment
		☐ Number of patients that completed the study
		☐ Reasons for discontinuation of treatment
		☐ Number of patients that were lost to follow-up
		☐ Protocol violations from study as planned, reasons
• Baseline data	10	☐ Demographic and clinical data, in tabular form
• Data analysis	11	☐ Number of patients included in each analysis
		☐ All eligible, enrolled patients need to be accounted for (intent-to-treat analysis).
		☐ Confidence intervals for primary and key secondary end points
		☐ Comparison with historical controls if formal analysis planned
• Outcome	12	☐ Summary of results for primary and secondary outcomes
		☐ If response rate is an end point and various histologies or grades are eligible, note the tumor type with responses.
		☐ Kaplan-Meier graph for progression/survival, depending on end points of the study
• Ancillary analyses	13	☐ Summary of other analyses performed and whether prespecified or exploratory (e.g., PK results
Discussion		
• Interpretation	14	☐ Interpretation of results taking into account study hypotheses, sources of potential bias, limitations, or weaknesses of the study
		☐ Comparisons with historical controls
• Expected versus observed	15	☐ Discussion of results in the context of what was expected and what was actually seen
• Overall evidence	16	☐ Include general interpretation of the results in context of current evidence and theory
• Future directions	17	☐ Based on results, is the therapy sufficiently efficacious to justify further study/research?
		☐ Future directions for the agent studied, if any
Acknowledgments		
• Disclosure	18	☐ Financial disclosure and any potential conflict of interest of the authors
		☐ Trial sponsor

Abbreviations: AdEERS, Adverse Event Expedited Reporting System; EIAEDs, enzyme-inducing antiepileptic drugs; IRB, institutional review board; PK, pharmacokinetic

*Not all checklist items will apply to all studies. Several checklist items have been taken from the CONSORT statement (Altman et al., 2001) with permission (also available at http://www.consort-statement.org).

Methods

The Methods should clearly present the population included in the study determined by eligibility criteria, the treatment plan, and the plan for management of patients during experimental treatment. A thorough understanding of the population studied is necessary for data interpretation. The method for assessment of specific outcome measures (toxicity for **phase 1** trials, and safety, feasibility, and efficacy for **phase 2** trials), as well as the statistical considerations used in the design of the study, must be clearly presented. With this information, the feasibility of the treatment plan and the interpretation of the results can be evaluated.

Item 4. Eligibility Criteria: Specific Factors Influencing the Outcome of Neuro-Oncology Clinical Trials. As patients' characteristics can affect the evaluation of toxicity or efficacy, it is vital that these characteristics be clearly presented. A statement that all patients gave informed consent and that the study was approved by the supervising Institutional Review Board should be included. For **phase 1** studies, factors such as age, general medical health, performance status, normal organ function (determined by specific laboratory tests), and concomitant medications can alter the trial drug's toxic effects, and these factors should be clearly noted. For **phase 2** studies, eligibility criteria that relate to prognostic characteristics (e.g., age, performance status, staging when appropriate for tumor type, extent of residual disease, and prior treatment) of the patients studied must be reported, as hidden selection bias can distort the interpretation of the efficacy of the trial drug. Enrollment restrictions based on the patients' disease status at the time of study entry, especially for phase 2 efficacy studies, should be noted, for example, number of relapses or number of prior therapies or regimens allowed. For instance, many phase 2 studies of malignant glioma specify that patients must be in their first relapse to be eligible.

For studies performed at the time of recurrent disease, radiological documentation of progression must be defined. Histological confirmation of the diagnosis is necessary for predicting clinical behavior of a tumor and determining appropriate treatment; however, some tumor locations—for example, the brain stem—may be prohibitive for biopsy. Accurate histological classification is especially important when the assessment of antitumor effect is an objective of a study. Unfortunately, many previously used grading systems exist for brain tumors, making it difficult to perform interstudy comparisons in much of the literature. The 2000 WHO classification is now accepted as the current system used to classify CNS tumors and should be referenced (Radner et al., 2002). Vague terms such as *malignant glioma*, which can include anaplastic astrocytomas, anaplastic oligodendrogliomas, and glioblastomas, should be avoided.

Because of the difficulties of interobserver variability and subjectivity in classifying brain tumors, especially grade II and grade III gliomas (Scott et al., 1995), central pathology review is highly recommended for **phase 2** studies and should be noted if performed. This is especially important for characterizing the study cohort reliably in **phase 2** studies, in which relatively small numbers of patients are enrolled as compared to a randomized, controlled phase 3 trial. Another factor to consider is that most studies allow patients to be included in trials on the basis of their original histological diagnosis even when there has been obvious tumor progression since the original treatment and a possible change in the grade of the tumor. A report should specify if patients qualified for the trial at the time of reoperation, at which time a more recent histological sample would dictate the patient's eligibility. For example, origin of the histological specimen may be important for studies of primary or secondary glioblastoma, where the biology and response to experimental agents may be different (Kleihues and Ohgaki, 1999).

Patients' characteristics that may be used as independent variables in analysis of the results—either prognostic factors (including molecular genetics, such as 1p and 19q for oligodendroglioma or O^6-methylguanine-DNA methyltransferase for glioblastoma) or concurrent use of some medications—should be noted.

Item 5. Treatment Plan. There must be a clear presentation of the treatment plan. The dose, schedule, method of treatment delivery, definition of a treatment cycle, and the planned duration of therapy with criteria for removal from the study should be specified. If the treatment includes concurrent irradiation, the authors should note the details of the dose, the fractionation schedule, the number of fractions, and the target volume, including modifications based on the sparing of critical structures. All the requirements and restrictions for treating a patient enrolled in the study should be included in this section.

Toxicity/adverse events. The criteria for toxicity assessment, measured by using the current version of the NCI Common Terminology Criteria for Adverse Events (NCI, 2003), should be stated, as well as plans for monitoring and responding to adverse events. Guidelines used for reporting adverse events, such as AdEERS, the NCI Adverse Event Expedited Reporting System (NCI, 2005), should be noted.

Dose escalation/reduction. Dose escalation and reduction are relevant to **phase 1** and some **phase 2** studies. The dose escalation plan, including the definitions of dose-limiting toxicities and the maximum tolerated dose, should be described. The data safety monitoring plan should be explained briefly, and the conditions for replacement of patients should be clear.

Item 7. Assessment of Efficacy. Assessment of the drug's efficacy is the primary goal of **phase 2** studies, and **phase 1** studies often look for preliminary evidence of activity. The rationale for the end point chosen for assessing efficacy must be noted (Haines, 2002). If objective tumor response is used as an end point, the methods for assessing changes in tumor size or physiologic parameters should be clearly reported, as should the criteria for declaring response or progression using

clinical or radiographic means (including when the first follow-up scan is to take place, what parameters are included, the timing of follow-up evaluations, and steroid dosing requirements) (Cairncross et al., 1988; Macdonald et al., 1990). Because variations in imaging timing, position, and technique can lead to significant variability in evaluation, central review of response is recommended and should be noted if incorporated into the study. Methods for assessing the potential impact of interventions other than the experimental intervention on neuro-imaging should be discussed, such as control of corticosteroid use, prior radiation (including stereotactic radiosurgery), and intratumoral therapies, as well as the time interval from prior interventions. This information will assist the reader in interpreting neuro-imaging results.

For brain tumor patients, for whom time to progression is often short and objective evaluation of tumor size is usually impossible between scheduled imaging times, the difference between no effect on time to progression and a 33% prolongation of time to progression could go undetected during a single interval between imaging. When a trial is nonrandomized and there are no placebos, the time-to-progression end point can rarely be considered free from considerable potential for bias. For this reason, six-month progression-free survival or a similar milestone end point (with imaging performed at that time) may be preferable. If end points such as time to progression or six-month progression-free survival are used, the nature and frequency of evaluation methods used to assess tumor growth should be reported. Many pediatric tumors are more responsive to therapy, and therefore, in pediatric studies, six-month progression-free survival or other benchmarks of progression-free survival may not be as important as the end points of overall survival or disease-free survival.

Item 8. Statistical Methods. For **phase 1** studies, the statistical considerations are limited, given the small sample size, and depend on the dose-escalation plan chosen for the study. For **phase 2** studies, the hypothesis, justification of the sample size needed to determine whether the treatment was a success, parameters for defining success (with a plan to provide estimates of confidence intervals), study design, and methods for statistical analysis should be clearly stated. Concise descriptions of statistical methods for phase 2 oncology trials are available in the literature (Lee and Feng, 2005; Mariani and Marubini, 2000; Simon, 1989). Stopping rules should also be explained. For the assessment of treatment efficacy, the use of a historical control group may be informative (Hess et al., 1999; Lamborn et al., 2004; Wong et al., 1999). Having a prognostically similar historical control group is ideal, and reference to the historical control group selected should be provided. The same inclusion and exclusion criteria that are applied to patients receiving the study agent must be applied to the controls, to avoid bias that could be introduced in the patient-selection process. Since trials of locally delivered therapies (e.g., intratumoral therapies) have exclusion criteria that inevitably relate to the size and location of the tumor, these trials are especially vulnerable to excluding the patients with the worst prognosis, who are not excluded in most historical control series. There are many examples in the literature, including studies of intra-arterial BCNU, brachytherapy, and stereotactic radiosurgery, where the ultimately disappointing outcomes of large, randomized trials could have been predicted with appropriate adjustment of the observed phase 2 results for the exclusion of poor-prognosis patients (Irish et al., 1997; Kirby et al., 1995). More effort has to be made to identify appropriate control groups with similar exclusion criteria for phase 2 surgically based trials.

Any rules used to determine end points should be defined. The handling of missing data must be addressed.

Results

Any deviations from the initial study plan (e.g., number of patients) should be explained.

Item 12. Outcome

Toxicity. In general, treatment-related nonneurological toxicities are not difficult to identify in patients with brain tumors. In contrast, study agents may have neurological toxicities that are difficult to distinguish from cerebral edema, effects of concomitant medications, or the effects of the tumor. For example, a seizure may be caused or influenced by the study drug, but alternately might be due solely to a preexisting seizure disorder, tumor progression, or lack of adequate treatment with anticonvulsants. Consequently, in **phase 1** trials, it is important to determine whether the patients are experiencing neurological toxicity caused by the new agent, by preexisting neurological causes, or by tumor progression. If the toxicity is thought to be due to compromised neurological status and not the study agent, adverse events should be reported in the context of the patient's preexisting neurological condition. If the study agent is thought to be responsible, this needs to be conveyed clearly. Careful analysis of observed toxicities will ensure that a study drug is not inappropriately blamed for adverse events and the study inappropriately halted, as well as ensure that a toxicity caused by the study drug is not attributed to other factors.

Phase 2 studies can provide more information on the acute toxicity profile of the study drug as well as data on cumulative or delayed toxicity of the agent. All adverse effects experienced by patients while enrolled in the study, including those attributed to the experimental therapy, should be presented in tabular form for easy reference. For **phase 1** studies, the determined maximum tolerated dose should be clearly stated.

Efficacy. **Phase 1** studies are only exploratory in terms of activity. Authors need to be cautious in making statements of efficacy based on small numbers of patients and should acknowledge statistical limitations.

Statements of efficacy in **phase 2** trials must take prognostic factors into account. When necessary, prognostic factors should be summarized by subgroups (e.g.,

histology). Independent adjudication of response claims should be performed by an experienced neuroradiologist unassociated with the study or the study sponsor. The authors should include 95% confidence intervals for response rate and for key end points such as time to progression, median survival, and overall survival, to highlight degree of precision in estimates and potential clinical significance of the results. This is especially important for negative studies.

Intent-to-treat analysis. One of the most common problems in interpreting and comparing **phase 2** outcomes from different studies, and a probable reason why **phase 2** results may poorly predict the outcome of larger trials, is the exclusion from the evaluable cohort the patients who do not complete a specified number of courses of the agent or regimen. This automatically depletes the series of the patients with the worst prognoses, because many of the reasons for not completing planned therapy are related directly or indirectly to tumor progression. Moreover, many of the historical series that are used as explicit or notional comparators consist of all patients in a cohort and have not been subjected to similar exclusions. We strongly recommend that primary **phase 2** analyses be based on intent-to-treat analysis: Include all patients started on the treatment, even those who did not complete a cycle, or were lost to follow-up, and arguably even those who died from seemingly unrelated causes. The minimum desired effect rate can be set prospectively to anticipate this kind of analysis (e.g., 15% odds ratio, instead of 20%). Then, if the trial can be reported as positive, taking into account all enrolled patients, it becomes scientifically acceptable to report secondary analyses that exclude patients who did not receive the full duration of the treatment, as this can be potentially helpful in assessing the upper boundary of the expected benefit in a larger population.

Discussion

The discussion should summarize the relevant findings, limitations of the findings, and the generalizability of the conclusions. Comparisons to other reported studies of the drug or related agents should be made. Further directions for the study drug should be proposed, based on the results.

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